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Efficacy of 8% arginine on dentin hypersensitivity: A multicenter clinical trial in 273 patients over 24 weeks

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Abstract: OBJECTIVES To assess the efficacy of 8% arginine containing prophylaxis products over 24 weeks in subjects with dentin hypersensitivity (DH). METHODS 297 patients with established DH (Schiff score 2, 3) in three European study centers were randomly assigned to either 8% arginine and calcium carbonate in-office prophylaxis paste and the respective toothpaste (test group) or fluoride-free prophylaxis paste and sodium monoflourophosphate toothpaste as a negative control group. Air blast (Schiff Score) and tactile (Visual Analog Scale) sensitivity scores were assessed at baseline (BL_0), $after single application of$ $home use of the toothpaste. RESULTS 273 subjects completed the study. Test and control group presented statistically signifi$ $test, p < 0.05) in Schiff Score at BL_1 and at 24 weeks relative to BL_0 (difference in\%; test group: -23.6, -44.9, control group$ $-8.8, -32.7). The pooled Schiff Score for the two evaluated teeth yielded a significantly greater alleviation of DH in the test gr$ $0.05; difference in\% : 15.3, 7.4, 10.6, 17.2). CONCLUSIONS A significant relief of DH was demonstrated after applicatio$ $lasting treatment methods in order to manage their patients' discomfort.$

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Efficacy of 8% arginine on dentin hypersensitivity: A multicenter clinical trial in 273 patients over 24 weeks.

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Abstract

Objectives: To assess the efficacy of 8% arginine containing prophylaxis products over 24 weeks in subjects with dentin hypersensitivity (DH).

Methods: 297 patients with established DH (Schiff score 2, 3) in three European study centers were randomly assigned to the application of either 8% arginine and calcium carbonate in-office prophylaxis paste and the respective toothpaste (test group) or fluoride-free prophylaxis paste and sodium monoflourophosphate toothpaste as a negative control (control group). Air blast (Schiff Score) and tactile (Visual Analog Scale) sensitivity scores were assessed at baseline (BL_0), after single application of the prophylaxis paste (BL_1) and after 4, 8, and 24 weeks of continuous at-home use of the toothpaste.

Results: 273 subjects completed the study. The test and the negative control group presented statistically significant percentage reductions (t-test, $p<0.05$) in Schiff Score at BL_1 and at 24 weeks relative to BL_0 (difference in %; test group: -23.6, -44.8, control group: -8.8, -32.7). The pooled Schiff Score for the two evaluated teeth yielded a significantly greater alleviation of DH in the test group than in the control group at all evaluation appointments (Ancova, $p<0.05$; difference in %: -15.3, -7.4, -10.6, -17.2).

Conclusions: A significant relief of DH was demonstrated after application of the 8% arginine prophylaxis paste and respective toothpaste over 24 weeks compared to a negative control product.

Clinical significance: Whilst DH is influencing patients' eating, drinking and tooth brushing habits as well as social life interactions it is important that clinicians are able to offer evidence based immediate and long-lasting treatment methods in order to manage their patients' discomfort.

Introduction

Dentin hypersensitivity (DH) is a frequently observed pain condition worldwide [1–5]. A short sharp pain in response to thermal, evaporative, tactile, osmotic, or chemical stimuli is symptomatic for DH [6]. This acute pain condition typically occurs when the cervical dentin surface becomes exposed following the loss of enamel or the recession of the gingiva with concurrent loss of cementum [7, 8]. As gingival recession was found in approximately 80% of the population [9, 10] it may be an important predisposing factor for DH [11].

Many factors for the hard tooth substance loss such as abrasion, abfraction and erosion are discussed in the multifactorial etiology [12]. A thorough anamnesis and differential diagnosis are mandatory to identify the etiological factors and to exclude other tooth or soft tissue related pathologies [13].

DH affects the adult population and the prevalence rates range from 3 to 98% [5, 14, 15]. The heterogeneity derives from differences in the selection criteria of the study population and the diagnostic methods used [14]. Previous studies have demonstrated that 46% of 18–77 years old people suffer from DHS [7] and that especially younger populations can be affected with up to 42% of the 18–35-year-old experiencing sensitivity [8]. Furthermore, periodontitis patients are reported to have a higher prevalence of DH as the root surface may become exposed as part of the disease process and treatment course [16, 17]. Root sensitivity has been shown to raise from 9-23% up to 54-55% one week after non-surgical periodontal therapy [18] and to be transient in duration [19].

Up to date, the “hydrodynamic theory” of Brannström still serves as the most plausible and widely accepted physio-pathologic mechanism [20]. In dentin tubules, which are patent to the oral cavity, external stimuli can induce an outward and/or inward flow of dentin fluid. Thus, pulpal baroceptors are activated and trigger the pain sensation [20].

Although abundant research about DH exists, there is still some uncertainty regarding the exact pain mechanism [21]. However, from a clinical perspective, two prerequisites are necessarily required for DHS to occur, namely non-carious dentin exposure [22] and contiguous dentin tubules patency from the pulp to the oral cavity [23]. Consequently, any therapy of DH should interact with the hydrodynamic sequence either at the surface of the patent dentin tubules or within the neural

transmission pathway at the dentin/pulp border [22]. Therefore, a plethora of possible cause-related treatment agents and methods was intensely studied during the last 50 years leading to a large number of products being actually available on the market [24]. So far, clinical effectiveness has been proven to some extent for stannous fluoride, arginine, calcium sodium phosphosilicate and strontium toothpaste [24]. However, no treatment option can be qualified as gold standard, which could lead to a predictable and long-lasting relief of DH yet [11].

In recent years, arginine combined with calcium carbonate was introduced and postulated to be a new breakthrough technology [25]. Both, arginine and calcium carbonate are naturally available in human saliva. In combination with calcium carbonate and phosphate the positively charged glycoprotein arginine forms deposits on negatively charged exposed dentin surfaces, which are able to seal the open tubules and block the fluid flow mechanically [26]. Thereby, the natural process of plugging dentin tubules is enhanced [27]. The body of evidence to bring rapid and considerable relief of DH is high when applied as a toothpaste twice daily and compared to a negative control or other desensitizing products [24]. Three studies – from one single research group – report sensitivity scores over 8 weeks using a 8% arginine containing dentifrice twice daily compared to a fluoride containing toothpaste. Results show a significantly higher alleviation of DH in the test group [28–30]. One study in a US-population by Hamlin and co-workers questioned the long-term effects of arginine over 24 weeks. The results showed an instant and long-lasting improvement in tactile and air blast sensitivity scores in the test group which were significantly superior to the results in the control group [31]. Single in-office application of a 8% arginine containing desensitizing paste has proven to be effective [32, 33], nevertheless the evidence is weak [24]. Studies combining in-office and at-home regimens over 24 weeks, however, are still scarce.

Therefore, this study was designed to evaluate the efficacy of prophylaxis products containing 8% arginine on the change in pain related parameters (air blast sensitivity as measured with the Schiff score and tactile sensitivity as measured with the Visual Analog Scale (VAS)) compared to a negative control in a large, multinational study sample with established DH over 24 weeks. The hypothesis was that the test agents lead to more reduction in immediate and long-term DH parameters.

Methods

The present clinical trial was performed as a randomized, double-blinded, multicenter study with a parallel group design including a negative control arm. Three independent centers from three European countries participated in this study, namely France (Clermont-Ferrand), Germany (Halle) and Switzerland (Zürich).

Ethical considerations

The study was performed in compliance with ISO 14155 (2011), Good Clinical Practice (GCP), and the Declaration of Helsinki of 1975, as revised in 2008 and the study protocol was approved by the ethic committee of each participating university. As required, each patient was verbally informed in detail about the trial and written informed consent was obtained and signed prior to inclusion. Patient names as well as all other personal data were kept under strict confidence by the investigator, the monitor and all included authorities.

Patient population

The patient sample (298 patients were screened and 297 were selected) was recruited between January 2012 and December 2014 in the three study centers. Different patient recruitment options were chosen by the three centers, among them were newspapers advertisements, Facebook advertisements, recruitment at dental schools, schools for dental hygienists and the university dental clinics.

The patient inclusion criteria were as follows: (1) age from 18-70 years, (2) male or female subjects, (3) at least two non-molar teeth with a diagnosis of DH in relation to cervical dentin exposure and with a Schiff score 2 or 3 following an air blast stimulus applied for one second to the exposed surface, (4) good general health and (5) availability for 5 appointments during the 6-month duration of the study. The exclusion criteria were set as follows: (1) gross oral pathology, (2) periodontal disease or treatment within the past twelve months, (3) hypersensitive teeth with buccal restorations, caries or cracked enamel lesions, pulpitis, abnormal occlusal

forces due to bruxism, advanced erosion/abrasion, orthodontic bands or mobility greater than one and teeth serving as abutments for fixed or removable restorations or fixed full prosthetic crowns, (4) use of any desensitizing product within the past 3 months, (5) current participation in any other clinical study within the last 12 months prior to enrolment, (5) pregnant or lactating women, (6) known allergies to the test products or other personal care consumer products, (7) existing medical conditions which prohibits not eating and drinking for 4 hours prior to each study visit, (8) any chronic disease, (9) medication with anticonvulsants, antihistamines, antidepressants, sedatives, tranquilizers, anti-inflammatory drugs, daily analgesics within one month prior to the start of the study or during the course of the study.

Sample size calculation

Sample size calculation was performed upon the primary efficacy endpoint (Oral Health Impact Profile (OHIP)–49), which will be reported in a separate paper. By means of the inclusion of 286 patients the clinically relevant difference of 6 points between the test group and the control group after 6 months can be detected with 80% power by a t-test to the 5%-level. To allow for some drop-out, 300 patients (150 per arm) were planned to be included.

Randomization and blinding

Randomization was performed as a stratified randomization for the two strata, i.e. Schiff score 2 and 3, respectively. Therefore, a balanced inclusion of Schiff score 2 and 3 participants could be achieved across the centers and groups. Additionally, the randomization was done (permuted) block wise. A number was assigned to each enrolled patient following the recruitment date. Sequentially numbered boxes with the blinded study products were used to maintain examiner blinding.

Data collection

Subjects, who identified themselves subjectively of having hypersensitive teeth, were screened for the inclusion criteria as mentioned above. Subjects eligible for the study

underwent the enrollment visit to assess for their anamnestic, demographic data and their oral health. After obtaining the written informed consent form, each patient was randomly assigned to the test and the control group.

In this multi-center trial, Schiff scores and VAS values were evaluated as secondary outcomes and are reported here. Measurements were performed as follows: for the Schiff score the respective tooth was isolated and protected towards the mesial and distal aspects with placement of the examiner's fingers over the adjacent teeth. Air was delivered from a standard dental unit air syringe at 60 ± 5 psi and 67-73°F for 1 second from a distance of 1 cm. The subsequent pain response through verbal and facial expression of the patient was immediately classified according to the Schiff score into 0 to 3 (0: did not respond; 1: responded but did not ask for discontinuation; 2: responded and asked for discontinuation or moved away; 3: responded, moved away and considered stimulus to be painful) [34].
The VAS values were assessed by the use of a calibrated periodontal probe (Aesculap DB764R) which allows for the application of a pre-set force of 25 g. The instrument tip was stroked twice back and forth perpendicular to the tooth surface within the first mm below the cemento-enamel junction. The patients were then asked to mark their perceived level of discomfort on the VAS between no pain (0) and worst pain (100) on the 100mm line [35].

Product management

The study products were supplied to the study centers at the beginning of the study and were delivered in cartons labeled with the center code and the randomization code for each patient to be included. Study products consisted of two cups of prophylaxis paste (test or control) packed in small neutral white boxes and 6 tubes (one for each month of the study duration) of 0.75 ml toothpaste (test or control) filled in neutral white tubes labeled with the patient code.
The prophylaxis paste for the test group was Elmex® Sensitive Professional™ desensitizing paste containing 8% arginine and calcium carbonate without fluoride (Colgate-Palmolive Co., New York, NY, USA) and the respective toothpaste, i.e. Elmex® Sensitive Professional™ desensitizing toothpaste with 8% arginine and

1450ppm fluoride as monofluorophosphate (Colgate-Palmolive Co., New York, NY, USA).

The prophylaxis paste for the control group was Nupro® pumice based fluoride-free prophylaxis paste (Dentsply Professional, York, PA, USA) and the corresponding toothpaste a sodium monofluorophosphate toothpaste with 1400 ppm fluoride, which was produced by the company as a negative control toothpaste exclusively for this study.

At baseline, the prophylaxis paste was applied in 2 consecutive 3-second applications at the gingivo-facial third of all teeth of the dental arch using a Kerr rotary white cup (Kerr, Bioggio, Switzerland) with low to moderate speed. Application was perfomed by a trained operator other than the investigator as the pastes were different in color and thus not blinded. At the end of the appointment participants were instructed for the individual at-home use of the toothpaste using a pea-sized amount of the assigned toothpaste to brush at least twice per day for 2 minutes for 24 weeks. One 75 ml tube was supplied for each month. All subjects received 6 toothbrushes and were instructed to brush their teeth with a soft-bristle Elmex® Sensitive Professional™ desensitizing toothbrush (Colgate-Palmolive Co.,New York, NY, USA) using the Stillman technique. Participants were requested to return all products to check for compliance.

Patient management

At the enrolment visit, the two DH study teeth were determined using the Cold Air Sensitivity Scale (Schiff Score). At baseline, the prophylaxis paste was applied in two consecutive three-second applications at the gingiva-facial third of the teeth of the whole dentition with a rotary cup. Before (BL_0) and immediately afterwards (BL_1) Schiff scores and VAS values were assessed to investigate the immediate impact of the prophylaxis paste.

Afterwards each patient was instructed to use the assigned toothpaste and tooth brush. After 4, 8 and 24 weeks of self-administered at-home dental care the patients were rescheduled for study visits to reassess the air blast and the tactile stimulated

hypersensitivity scores again. At each study visit patients were asked for changes in medication, general health status, dental status and adverse events.
Subjects had to refrain from all other oral hygiene procedures like rinsing, professional dental cleaning during the course of the study and chewing gum for 8 hours and eating and drinking for 4 hours prior to each study visit.
One calibrated dentist was involved in subject examinations in each study center. Calibration for both sensitivity tests was performed in a theoretical calibration session and via a PowerPoint presentation describing all details with exemplary photographs of patients facial expression referring to each score of the Schiff scale. The study was performed under double-blind conditions. The subject, the investigator, the study monitor and the statistician were blinded to the study products.

Data management

All data collected in the case report files (CRF) of this study were entered into a blinded computer database. Audits were performed by one external monitor per center from an independent study monitoring site on a regularly basis to supervise compliance with the study protocol and control the data management.

Statistical analyses

Analysis was done on the eligible intention-to-treat population. Descriptive analyses were calculated to depict the demographic data (age and sex) for each study group. Statistical analyses were performed separately for the Schiff scores and VAS values. Subject-wise mean scores were calculated by averaging the values obtained from the two study teeth designated at the enrollment visit.
Mean values and standard deviation (± SD) were calculated for the Schiff scores and the VAS values at BL_0, at BL-1 and at 4, 8 and 24 weeks.
Intergroup comparisons were performed on the mean values at the different time points (BL_1, 4, 8 and 24 weeks) using an oneway analyses of covariance (ANCOVA) adjusted to BL_0 measurements as well as to age and sex.
Furthermore, the intragroup comparisons for the differences between baseline and the follow-up visits were performed using the paired Wilcoxon signed-rank test.

A commercially available statistical software program was used (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). All statistical tests of hypotheses were two sided and employed a level of significance of 5%. The analyses of all endpoints obeyed to the intention-to-treat principle.

Results

Two-hundred-seventy-three patients (137 in the test and 136 in the control group) completed this 24-week clinical trial. Two-hundred-sixty-eight patients complied with the protocol. Five patients had to be excluded due to the inadequate toothpaste consumption. A summary of the demographic data is depicted in table 1. The two groups did not differ significantly with respect to age and gender characteristics. However, age groups were not equally distributed inside each group, since there were significantly more women than men included in the test and in the control group (79.4%and.77.4%, respectively).

The subject distribution displaying Schiff scores 2 and 3 at screening was similar in the two study groups. Teeth were summarized per patient and the mean value was used for the subject-based analyses.

Air blast sensitivity evaluation

Table 2 presents the data of the mean Schiff score at each time point per group. The mean score at BL_0 in the test group was 2.54 ± 0.42 and in the control group 2.51 ± 0.48 showing an equal distribution of subjects with Schiff scores 2 and 3 in both groups. A comparison between the groups revealed no statistical significant difference (p=0.616).

At BL_1, the mean Schiff Score in the test group was 1.94 ± 0.71 and in the control group 2.29 ± 0.58, showing a significant reduction from BL_0 to BL_1 ($p<0.001$) in both groups. The difference between the two groups of -15.3% was significant ($p<0.001$). After the home-care treatment phase at 4-weeks the Schiff Score in the test group accounted for 2.01 ± 0.78 and was higher than at BL_1. However, this difference did not reach statistical significance (p=0.072). Up to 24 weeks the Schiff

score dropped to 1.40 ± 0.90, which was significantly reduced compared to the Schiff score at BL_1 as well as at the 4- and 8-week time points ($p<0.001$). Expressed in percentage, the difference reflected a -23.6% reduction from BL_0 to BL_1 and a -44.9% reduction from BL_0 to 24-weeks.

The control group showed a significant stepwise reduction with regard to Schiff scores to 2.17 ± 0.68, 1.99 ± 0.83 and 1.69 ± 0.94 at 4-weeks, 8-weeks and 24-weeks, respectively ($p<0.05$). Expressed in percentage, the difference accounted for a -8.8% reduction from BL_0 to BL_1 and a -32.7% reduction to 24-weeks.

The difference between the two groups at 4-, 8- and 24-weeks was statistically significant ($p=0.030$, $p=0.023$ and $p<0.001$, respectively) favoring the test group.

Tactile sensitivity evaluation

Table 3 presents the data of the mean VAS value (in mm) at each time point per group. The mean VAS value at BL_0 was 27.96 ± 25.11 in the test and 25.96 ± 24.75 in the control group. The comparison between these groups adjusted for gender and age revealed no statistically significant difference ($p=0.243$).

At BL_1, the mean VAS value adjusted for BL_ 0 was 17.69 ± 20.68 in the test group and 19.59 ± 21.82 in the control group, which reflected a significant reduction from BL_0 ($p<0.001$) in both groups. The difference between the two groups expressed in percentage showed a difference of -9.7%, which was statistically significant ($p=0.024$).

During the home-care treatment phase after 4- and 8-weeks the VAS value in the test group was 19.04 ± 21.77 and 15.43 ± 19.10 without statistically significant difference to BL_1 ($p=0.129$ and $p=0.169$ respectively). After 24 weeks, the VAS value dropped to 11.89 ± 16.62, which reflected a statistically significant change as compared to the VAS value at BL_1 ($p=0.005$) as well as at the 4- and 8-week time points ($p=0.03$ and $p=0.037$, respectively). The differences in percent showed a -36.7% reduction from BL_0 to BL_1 and of -57,5% from BL_0 to 24-weeks.

The control group showed a non-significant reduction in VAS values to 17.17 ± 18.88 after 4-weeks ($p=0.173$) and to 17.31 ± 19.71 after 8-weeks ($p=0.079$) with regard to BL_1. After 24-weeks the VAS value was significantly reduced to 14.15 ± 17.36 ($p=0.005$) as compared to BL_1. The difference between the test and the control

group was, however, not significant at any of the time points (p=0.563, p=0.219 and p=0.185, respectively).

Discussion

This study assessed the efficacy of an in-office desensitizing paste and the respective toothpaste, both containing 8% arginine and calcium carbonate in achieving instant and sustained relief on hypersensitivity over a 24-week period in patients suffering from DH. The results were compared to a pumice-based fluoride-free prophylaxis paste and a sodium monofluorophosphate toothpaste (control group). Hypersensitivity evaluation was performed at baseline before and after application of the desensitizing paste and at 4-, 8- and 24-weeks by using the Schiff-score after air blast stimulation and the VAS after tactile stimulation.

Due to the used stratification protocol both groups were comparable at baseline. The statistically significant reduction of hypersensitivity in the test group after the application of the prophylaxis paste revealed the efficacy of the 8% arginine formula to immediately alleviate DH about approximately one fourth (-23.6%). The control group presented as well with a statistically significant but lesser hypersensitivity reduction (-8.8%). Nevertheless, the statistically significant difference between the two groups demonstrated the higher efficacy of the arginine and calcium carbonate products, which might be rated as clinically relevant.

Between baseline and the 4-week examination, the Schiff score revealed no further statistically significant DH reduction in the test group. This might eventually be attributed to the fact, that the maximum plugging effect on the hypersensitive areas has yet been achieved with the initial arginine application. The 8- and 24-week Schiff score demonstrated again a significant DH reduction in the test group. The overall effect in the test group may be attributed to the continuous at-home use of the 8% arginine and calcium carbonate toothpaste.

The pumice-based fluoride-free prophylaxis paste and the sodium monofluorophosphate toothpaste have also been used as control products in recent studies [32, 33]. As they do not contain any further desensitizing agents, they may be considered as appropriate control products. Nevertheless, the latter showed also statistically significant immediate DH reduction after application of the prophylaxis

paste as shown in other studies [32, 33]. The reason for this effect may be attributed to the placebo-induced analgesia, which has an important impact on the treatment of pain in general and might be beneficial in the alleviation of the symptoms of dentin hypersensitivity [11]. Placebo products can reduce sensitivity by as much as 40% from baseline and thus influence the ability to differentiate the efficacy of a test product [36, 37]. The Hawthorne effect resulting from the high intensity of care due to 6 study visits might as well positively influence the outcome in both groups [38]. Another factor eventually influencing the DH reduction might be the use of a soft-bristle toothbrush and the instruction of the gentle Stillman technique.

As possible shortcoming of the study, a missing positive control should be mentioned, which should have been included following the criteria of Holland et al. [6]. As a possible agent, potassium was often used as positive comparator, however the effectiveness of potassium itself has to be questioned [24]. Other clinically effective treatment options like toothpastes with stannous fluoride, calcium sodium phosphosilicate or strontium [24] could have also served as a positive comparator. Another shortcoming was the lack of the control for the influence of the nutrition. It is known, that tubule occlusion of desensitizing agents has to withstand the daily acidic dietary challenge. Dietary habits differ from one individual to the other and thus impact the efficacy of the study product [24]. However, the strengths of the present study were the large patient sample size and the inclusion of three centers in three different European countries.

The tactile stimulus as measured by the VAS did reveal a significant amelioration of the DH in each of the two groups as well, however it did not reveal a significant difference between the control and the test group. In this context, it should be considered, that pain from hypersensitive dentin can be provoked more frequently by an air-blast than by a tactile stimulus [5, 18]. Consequently, the air blast test seems to be the more sensitive test method. However, Pepelassi and co-workers found a strong correlation in their study on hypersensitive teeth in periodontitis patients between the two methods and thus recommended their combined use for further studies [17].

This highlights the necessity of the use of two different clinically relevant stimuli to evaluate and monitor pain from hypersensitivity. Holland et al. set out the guidance in 1997 to choose two test methods out from the air-blast, tactile or thermal stimuli [6]. Finally, the measurement of DH is subjective, as it is based on the patient's reaction.

Thus, it is difficult to objectively measure and evaluate DH, even with the above mentioned established test methods.

The initial mean Schiff score of 2.54 and 2.51 in the test and control group respectively can be interpreted as an awkward event, which triggers the reflex to move immediately away from the painful stimulus. In the test group, a reduction to a mean score of 1.40 at 24 weeks reflects complete alleviation of painful hypersensitivity events. The stimulus is perceivable but not awkward any more. The pain alleviation thus shown by the Schiff Score approximates -45% over 24 weeks. The control group completed with a Schiff score of 1.69, meaning that there might still be some awkward stimulus leading to a request of discontinuation of the cold air blast. This figurative presentation of the results stresses the clinical relevance of the difference in DH due to the arginine containing test products.

Thus, it can be concluded that a single application of the 8.0% arginine containing prophylaxis paste and a continuous application of the 8.0% arginine containing toothpaste can be recommended to patients suffering DH. Further clinical studies with a larger sample size, a positive control and the use of only one product (prophylaxis paste or toothpaste) are needed to confirm these conclusions.

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Tables

	Number of subjects			Age distribution	
	Male*	Female*	Total	Mean**	Range
Test group	31	106	137	42.5	20-70
Control group	28	108	136	40.8	18-69
Total	59	214	273		

* No statistical difference was found between the distribution of the subjects with respect to gender (Fisher's exact test; p-value 0.769)

** No statistical difference was found between the distribution of the subjects with respect to age (t-test; p-value 0.272)

Table 1 Summary of age and gender for subjects who completed the 24-weeks clinical study (ITT population)

Treatment method	Evaluation time	Within and intergroup analysis				
		Mean ± SD (mm)			% difference between groups	
		Test		Control	% value	p-value
In-office treatment	Baseline_0	2.54 ± 0.42	0.000§	2.51 ± 0.48	1.2%	0.616*
	Baseline_1	1.94 ± 0.71		2.29 ± 0.58	-15.3%	0.000**
At-home care	4-weeks	2.01 ± 0.78 a)	0.000§	2.17 ± 0.68 b)	-7.4%	0.030**
	8-weeks	1.78 ± 0.79 a)		1.99 ± 0.83 b)	-10.6%	0.023**
	24-weeks	1.40 ± 0.90 b)		1.69 ± 0.94 b)	-17.2%	0.007**

* Significance of the Ancova intergroup comparison adjusted for age and gender.
** Significance of the Ancova intergroup comparison of the baseline_0 adjusted means.
§ p - values for the significance of the Wilcoxon signed-rank within group comparison.
a) $p > 0.05$; no statistically significant difference between 4- and 8-weeks respectively and baseline_1.
b) $p < 0.05$; statistically significant difference between 4-, 8- and 24-weeks respectively and baseline_1.

Table 2 Summary of the air blast sensitivity data evaluated with the Schiff Score at each time point per group

Treatment method	Evaluation time	Within and intergroup analysis				
		Mean ± SD (mm)			% difference between groups	
		Test		Control	% value	p-value
In-office treatment	Baseline_0	27.96 ± 25.11	0.000§	25.96 ± 24.75	7.7%	0.243*
	Baseline_1	17.69 ± 20.68		19.59 ± 21.82	-9.7%	0.024**
At-home care	4-weeks	19.04 ± 21.77 a)	0.000§	17.17 ± 18.95 a)	10.9%	0.563**
	8-weeks	15.43 ± 19.10 a)		17.31 ± 19.73 a)	-10.9%	0.219**
	24-weeks	11.89 ± 16.62 b)		14.15 ± 17.36 b)	-16.0%	0.185**

* Significance of the Ancova intergroup comparison adjusted for age and gender.

** Significance of the Ancova intergroup comparison of the baseline_0 adjusted means.

§ p - values for the significance of the Wilcoxon signed-rank intragroup comparison.

a) $p > 0.05$; no statistically significant difference between 4- and 8-weeks respectively and baseline_1.

b) $p < 0.05$; statistically significant difference between 24-weeks and baseline_1.

Table 3 Summary of the tactile sensitivity data evaluated with the Visual Analog Scale (VAS) in mm at each time point per group